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DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
EMCH, GREGORY S	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,540	TERKELTAUB, ROBERT	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *7 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-15* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *24 November 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1-15 are pending in the instant application. Applicant's election with traverse of the species of S100 proteins in the reply filed on 25 July 2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Furthermore, during a telephone conversation with Lisa Haile on 08 January 2007 a provisional election was made with traverse to prosecute the species of TRAF2. Affirmation of this election must be made by Applicant in replying to this Office action. Claims 7 and 14 are hereby withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected subject matter. This is because claim 7 recites a polynucleotide that inhibits tTGase or FXIIIa *expression,* not tTGase or FXIIIa *activity and/or activation*, whereas Applicant has elected a protein species i.e., S100 proteins to block activity and/or activation of tTGase or FXIIIa. Further, claim 14 is directed to the non-elected protein species.

Hence, claims 1-6, 8-13 and 15 are under examination in the instant office action.

Claim Objections

Claim 2 is objected to because of the following informalities: Claim 2 recites the limitation, "a member selected from the group ***consisting essentially of***' and is

therefore an improper Markush group. Applicant is advised that amending the claim recite language such as, "wherein the inhibition of activation is accomplished by blocking production of IL-1, IL-8, ... ***or*** S100 family of proteins" or "wherein the inhibition of activation is accomplished by blocking production of a member selected from the group ***consisting of*** IL-1, IL-8, ... ***and*** S100 family of proteins" would obviate the rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: inhibiting activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes, and wherein the inhibition of activation is accomplished by blocking production of a member selected from the group consisting essentially of IL-I, IL-8, nitric

oxide donor Noc-12, peroxynitrite generator Sin- 1, tumor necrosis factor *α* (TNF*α*), and S100 family of proteins (elected species).

Claims 1-6 and 8-10 are genus claims because the specification (and claims) do not set forth the structure of the multitude of molecular species, i.e., the potential inhibitors of production of S100 proteins, for example, that are encompassed by the claims. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, there is no identification of any particular portion of any particular structure that must be conserved to practice the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Further, although the claims recite a functional limitation, i.e., blocking production of the claimed protein species, with the exception of A20 (as disclosed at p.10 of the

specification, for example), the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed molecules. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods reciting A20, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods that recite A20, does not reasonably provide enablement for methods that recite any blocking agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims require the use of a broad genus of potential molecules, and as

stated above, Applicant has not described all of the common features of the genus such that the skilled artisan could identify individual members. As broadly claimed, the methods of the invention can comprise use of any number of molecules, e.g., nucleic acids, polypeptides including antibodies, small molecules or peptidomimetics. If one considers only a subset of the molecules encompassed by the claimed methods, e.g., polypeptides, the potential amino acid sequences encompassed by the claims have particular structures, the predictability of which is complex and outside the realm of routine experimentation. Since detailed information regarding the structural requirements of the multitude of potential amino acid sequences encompassed by the claims are lacking, and given the lack of working examples reciting any and all of the sequences encompassed by the claims, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, making said peptides or polypeptides and testing them for the claimed biological activity would constitute undue experimentation.

Accordingly, it is well known in the art that even two polypeptides differing in structure by only one amino acid residue can have completely different functions. For example, Mickle et al. (Med Clin North Am. 2000 May; 84(3): 597-607) teaches that cystic fibrosis (CF) is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CTFR) (p.597). In this polypeptide channel, a mutation of a single glycine to aspartic acid at position 551, gives rise to the CF phenotype. Also, a single phenylalanine deletion at position 508 gives rise to the CF phenotype, thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid

CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein.

Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and thus the architecture of an entire cell. For example, Voet et al. (Biochemistry. 1990. John Wiley & Sons, Inc. 126-129 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pp.126-128, section 6-3A and page 230, column 2, first paragraph). Also, Yan et al. (Science 290: 523-527, 2000) teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another. Thus, as outlined *supra*, the predictability of amino acid sequences that would function as claimed is complex and outside the realm of routine experimentation.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to practice the claimed invention, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass variant molecules, undue experimentation would be required of the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims recite suppressing a pathological condition in the preamble, but do not recite a patient population or an agent to be administered. Therefore, the omitted steps are: a selection step and an administration step.

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed 24 November 2004 is enclosed in this action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al. (citation N on IDS dated 24 November 2004), in view of Hashimoto et al. (citation H on IDS dated 24 November 2004).

Claims 1, 2, 5 and 8-10 are directed to methods for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: inhibiting activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes, and wherein the inhibition of activation is accomplished by blocking production of a member selected from the group consisting essentially of IL-I, IL-8, nitric oxide donor Noc-12, peroxynitrite generator Sin- 1, tumor necrosis factor α (TNFα), and S100 family of proteins (elected species). Claims 11-13 are directed to a method for identifying an agent that affects matrix calcification, comprising contacting a chondrocyte *in vitro* with a test agent under conditions for inducing matrix calcification, wherein the chondrocyte expresses FXIIIa and/or tTGase; and determining the effect of the test agent on matrix calcification, wherein an effect on matrix calcification identifies the test agent as an agent that affects matrix calcification.

The Nurminskaya et al. reference teaches that transglutaminase and FXIIIa are unregulated during chondrocyte hypertrophy and calcification (p.1135) and that these factors are implicated in apoptotic cell death mechanisms in chondrocytes (e.g., p.1136, ¶3, p.1142, ¶5), as in the instant claims 1 and 5. Further, the Nurminskaya et al. reference teaches chondrocytes from a chondrocyte-derived cell line (p.1136, ¶5), as in the instant claims 10 and 13. Although the teachings of Nurminskaya et al. suggest that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states, the reference does not explicitly teach such.

However, the Hashimoto et al. reference teaches that articular and meniscal chondrocyte apoptosis and abnormal articular cartilage matrix calcification and degradation are implicated in human osteoarthritis (pp.1632-1633), as in the instant claim 1. The Hashimoto et al. reference also teaches that future treatment options, (e.g., apoptotic inhibitors), would alleviate chondrocyte apoptosis and thus matrix calcification and degradation (p.1638, final paragraph). Additionally, the Hashimoto et al. reference teaches that mediators, i.e., inducers of necrosis and apoptosis in chondrocytes include IL-1, TNFα and nitric oxide (p.1632, ¶3), as in the instant claim 2.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the teachings of the Nurminskaya et al. reference with those of the Hashimoto et al. reference. The skilled artisan would have been motivated to combine in order to treat pathological calcification in cartilage, (e.g., in osteoarthritis), as taught by Hashimoto et al. (p.1638, final paragraph). The references teach both *in vitro* and *in vivo* methods

(entire documents); thus, the artisan would have been motivated to practice the methods both *in vitro* and *in vivo*, as in the instant claims 8 and 9. Further, the skilled artisan would have been motivated to identify agents that affect matrix calcification, (as the instant claim 11), as taught by Hashimoto et al. (p.1638, final paragraph). In addition, since the references both utilize expression vectors to express FXIIIa in chondrocytes (e.g., Nurminskaya et al., p.1137, ¶5), the skilled artisan would have been motivated to do so, as in the instant claims 12 and 13. The person of ordinary skill in the art would have had a reasonable expectation of success because both references suggest that methods of inhibiting tTGase and FXIIIa, and thus chondrocyte apoptosis, would suppress pathological calcification in cartilage matrix (entire documents).

Claims 3, 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al., further in view of Heyninck et al. (citation I on IDS dated 24 November 2004).

The claims are directed to methods for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: inhibiting activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes, wherein the inhibition of activation is accomplished by blocking TRAF2 (elected species) and TRAF6 (non-elected species) and by expressing A20 in chondrocytes.

The Nurminskaya et al. and Hashimoto et al. references teach as set forth above but do not explicitly teach blocking TRAFs nor do they teach expressing A20.

However, the Heyninck et al. reference teaches that cellular expression of A20 inhibits TRAF2 mediated NF-κB signal transduction (e.g., abstract), as in the instant claims 3, 4 and 6. The Heyninck et al. reference also teaches that the TRAF2 mediated NF-κB signal transduction pathway is implicated in apoptosis (p.1472, column 1).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the teachings of the Nurminskaya et al. reference with those of the Hashimoto et al. and Heyninck et al. references. The skilled artisan would have been motivated to combine in order to treat pathological calcification in cartilage, (e.g., in osteoarthritis), as taught by Hashimoto et al. (p.1638, final paragraph). Further, the skilled artisan would have been motivated to utilize A20 in chondrocytes because of the advantages of doing so, as taught by the Heyninck et al. reference (entire document). The person of ordinary skill in the art would have had a reasonable expectation of success because the references teach that the methods would work (entire documents).

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al., further in view of Studer et al. (Osteoarthritis Cartilage, 1999 Jul; 7(4): 377-9).

The claim is directed to a method for identifying an agent that affects matrix calcification outlined above, wherein the test agent is a nitric oxide synthase (NOS) inhibitor.

The Nurminskaya et al. and Hashimoto et al. references teach as set forth above but do not teach a NOS inhibitor.

However, the Studer et al. reference teaches that inhibitors of NOS relieve the inhibition of cartilage matrix synthesis that occurs in response to IL-1 (abstract). The Studer et al. reference also teaches that NO (as produced by NOS) induces apoptosis in articular chondrocytes and thus participates in the calcification that occurs during human osteoarthritis (p.377, ¶2).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the teachings of the Nurminskaya et al. reference with those of the Hashimoto et al. and Studer et al. references. The skilled artisan would have been motivated to combine in order to find agents to treat pathological calcification in cartilage, (e.g., in osteoarthritis), as taught by Hashimoto et al. (p.1638, final paragraph) and Studer et al (p.377). The person of ordinary skill in the art would have had a reasonable expectation of success because the references teach that the methods would work (entire documents).

Claims 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al., further in view of Gohr et al (citation E on IDS dated 24 November 2004).

The Nurminskaya et al. and Hashimoto et al. references teach as set forth above but do not teach the elected species of S100 proteins.

However, the Gohr et al. abstract teaches that S100 proteins are present in aging articular chondrocytes and S100 is a tTGase substrate in these cells.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the teachings of the Nurminskaya et al. reference with those of the Hashimoto et al. and Gohr et al. references. The skilled artisan would have been motivated to combine in order to treat pathological calcification in cartilage, (e.g., in osteoarthritis), as taught by Hashimoto et al. (p.1638, final paragraph). Further, the skilled artisan would have been motivated to block S100 production in chondrocytes because of the advantages of doing so, as taught by the Gohr et al. abstract. The person of ordinary skill in the art would have had a reasonable expectation of success because the references teach that the methods would work (entire documents).

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 9AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
18 January 2007

ELIZABETH KEMMERER
PRIMARY EXAMINER